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MORTALITY OF MUNITIONS WORKERS EXPOSED TO DINITROTOLUENE

FINAL REPORT

Richard J. Levine, Dragana A. Andjelkovich,
Sharon Kersteter, Earl W. Arp, Jr., Sandor A. Balogh,
Patricia B. Blunden, and Jonathan M. Stanley

Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina 27709

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Project Officer: CPT James W. Carroll
MAJ David L. Parmer
Health Effects Research Division
U.S. ARMY MEDICAL BIOENGINEERING RESEARCH AND DEVELOPMENT LABORATORY
Fort Detrick, Frederick, MD 21701-5010

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To determine whether the carcinogenicity of dinitrotoluene (DNT) in rodent bioassays had relevance for humans, we examined the mortality experience of exposed workers at two ammunition plants. Cohorts of 156 and 301 men who had worked a month or more during the 1940s and 1950s at jobs with opportunity for substantial DNT exposure were followed through the end of 1980. Numbers of expected deaths and standardized mortality ratios (SMRs) were computed, using mortality rates of U.S. white males as the standard. No evidence of a

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carcinogenic effect was found, but unsuspected excesses of mortality from ischemic heart disease were noted at both plants (SMRs 143 and 131: 95% confidence limits 65-234 and 107-187, respectively). Deaths from ischemic heart disease remained high even when compared to expected numbers derived using mortality rates of the counties in which the plants were located. Additional analyses revealed evidence of a 15 year latent period and suggested a relationship with duration and intensity of exposure. Epidemiological investigations of other heavily exposed populations are needed to confirm the etiological significance of the association between DNT and heart disease described here. Keywords:

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INTRODUCTION

Dinitrotoluene (DNT) is used principally as a feedstock or intermediate in the production of toluene diisocyanate, the building block of flexible polyurethane foam. Small amounts are expended to produce dyes, explosives, and propellants. DNT is also a captive intermediate in the manufacture of trinitrotoluene (TNT). The major military use of DNT is in single base powders, where it serves as a component of propellants for artillery and small arms and as a coating for small arms propellants.[1] DNT isomers are found as impurities in TNT and comprise about 1 percent of the finished TNT produced by continuous nitration and purification. Very little DNT, however, remains in TNT following the batch trinitration process.[2]

In man DNT exposure has been reported to cause dermatitis, methemoglobinemia and anemia, and acute toxic hepatitis.[3,4] Laboratory studies have shown that DNT administered in the diet of mice and rats can lead to cancers of the liver, gall bladder, kidney, and connective tissues.[5,6] In order to evaluate the possibility that DNT might cause cancer or other potentially fatal illnesses in humans, all occupational groups in the U.S.A. with present or past exposure were assessed in regard to the feasibility of conducting a retrospective cohort mortality study.

Workers at commercial chemical plants were not suitable for such a study on account of small numbers, inadequate records, or recent exposures. Since World War II, however, DNT had been manufactured or used at a number of government-owned, contractor-operated ammunition plants. Five plants had manufactured DNT: Alabama, Chickasaw, Kankakee (later a part of the Joliet Army Ammunition Plant), Plum Brook, and Weldon Springs. Eight had produced single base propellants - Alabama, Badger,

Chickasaw, Gopher, Indiana, Oklahoma, Radford, and Sunflower - for which DNT might have been used in certain compositions.[7,8] Only Badger, Indiana, Joliet (Kankakee), Radford, and Sunflower still exist.

Contractors who had operated the decomissioned plants were approached to learn if personnel records dating to the 1940s or 1950s might have been retained. It appeared that these had been destroyed. All existing plants were visited. Personnel records from the 1940s had been destroyed except at Radford. While records since the 1950s remain at all but Indiana, single base propellants had been produced at Sunflower only during the 1940s; and at Badger persons with substantial exposure to DNT during the 1950s are estimated to number no more than 20. Suitable cohorts of exposed persons, therefore, could be identified from personnel records of only two government ammunition plants: Joliet and Radford.

BACKGROUND AND METHODS

At the Joliet plant, located in Joliet, Illinois, DNT was manufactured and purified. Persons who had worked on the DNT lines were presumed to have had opportunities for exposure to mono- and dinitrotoluenes, nitric and sulfuric acids, and toluene. Individuals who had also held other jobs at the plant were most likely to have worked in TNT manufacturing. The crude DNT produced was the technical grade mixture of approximately 76% 2,4-DNT, 19% 2,6-DNT, and 5% other isomers. Following purification by "sweating", the material was reported to contain at least 98% 2,4-DNT and about 1% 2,6-DNT. The 2,6-isomer is thought to be largely responsible for the hepatocellular carcinomas, which developed in exposed rats.[9]

At the Radford plant, in Radford, Virginia, the purified DNT was used in certain single base propellant formulations. A large number of jobs provided varying opportunities for exposure to DNT as well as many other materials, including ethyl alcohol, ethyl ether, benzene, nitrated cellulose, 2-nitrodiphenylamine, diphenylamine, cyclotetramethylenetetranitramine, barium/potassium nitrates, dimethyl/diethyl/dibutyl/dioctyl phthalates, titanium/magnesium/cupric oxides, organic and inorganic lead compounds, tin, aluminum, graphite, carbon black, and cotton dust. None of the persons studied from the Radford plant had worked with TNT.

Batch processes had been used throughout both plants, and there was considerable potential for exposure of the skin and respiratory tract. Exposure magnitude and duration over a typical workshift (exposure intensity) were estimated using data derived from process records and the assessment of persons familiar with the operations. DNT-related jobs at Joliet - those on the DNT production lines - were judged by the authors to afford high levels of DNT exposure. Jobs at Radford were categorized by plant technical personnel according to opportunity for exposure: high, moderate, low, or none (cf. Appendix).

Both plants were opened in 1941, but personnel records for the Joliet facility were not available prior to 1951. All men who had worked in DNT production at Joliet for at least 30 days during the 1950s were enrolled in the study cohort. There were five DNT production jobs: DNT nitrator operator, DNT washer operator, and sweat house helper, operator, and leader. At Radford the cohort was comprised of men who had worked for 30 days or more during the 1940s and 1950s in the following jobs: screen

house helper and operator, coating house helper and operator, and finishing area operator - coating house or screen house. All had the potential for high DNT exposure with the exception of finishing area operator - screen house, which provided a moderate level of exposure. Women were not included in the study since only one woman would have qualified.

The mortality of the cohorts was followed from enrollment after 30 days of DNT exposure through December 31, 1980. Dates of death or dates when cohort members were last known to be living were ascertained using a variety of sources. These included plant personnel records, the Social Security Administration, the Veterans Administration, the National Death Index, state registrars of vital statistics and motor vehicles, and telephone surveys of study subjects and relatives. Of 156 men in the Joliet cohort, 120 (77%) are known to have been alive on January 1, 1981, and 31 (20%) died during the period of observation. Of 301 in the Radford cohort, 162 (54%) are known to have been alive on January 1, 1981, and 133 (44%) were deceased. The vital status of 5 persons (3%) at Joliet and 6 (2%) at Radford remains unknown. Except for 4 persons, who had died while serving with the armed forces and for whom casualty reports were received, death certificates were obtained for each of the deceased. Underlying and contributing causes of death were coded by a trained nosologist of the National Center for Health Statistics, according to the eighth revision (adapted) of the International Classification of Diseases (ICDA).

All of the Radford cohort and 39 of 156 in the Joliet cohort including all 31 deceased were known to be white. Race of the remaining members of the Joliet cohort could not be identified, but was presumed white. (At the time of the 1950 census only

6 percent of men living in the county in which the Joliet plant was located were of other races).[10] Expected deaths were determined by applying age- and calendar year-specific mortality rates for U.S. white males to the person-years of observation accumulated by the cohorts through December 31, 1980. A computer program of Dr. Richard Monson was used for this purpose.[11] Persons whose vital status at the conclusion of the follow-up period was unknown contributed years of observation until the date they were last known to be alive, usually the date they terminated employment at the ammunition plant. Numbers of observed and expected deaths were enumerated for each underlying cause, and the ratio of observed to expected was expressed as the percent of expected deaths, or "standardized mortality ratio" (SMR). Statistical significance was evaluated by computing chi square with 1 degree of freedom. The cumulative Poisson probability was calculated separately whenever the number of deaths was less than five. Statistical power was estimated using the method of Beaumont and Breslow.[12]

Of 13,441 person-years of observation for both plants combined, 4,837 occurred 20 or more years after entry into the cohorts. Each cohort member on average contributed 29 years of observation, was 29 years old when admitted to the study, and, if he died during the interval, was 57 years old at death.

RESULTS

The mortality experience of cohorts from both plants combined is given in Tables 1 and 2. Table 2 describes only mortality more than 15 years following cohort entry. In all, 164 men from the two plants had died, compared with 127 expected, using mortality rates for U.S. white males as the standard. The combined SMR of 129 for all causes of death is significantly high ($p=0.001$), and it increases after 15 years have

elapsed since entry into the study (SMR 140, p=0.00007). Elevated all-cause mortality appears to be due largely to increased mortality from diseases of the circulatory system (SMR 140, p=0.002) and from accidents, poisonings, and violence (SMR 191, p=0.0007). Observed and expected deaths from all other causes were approximately equal (49 observed, 50.4 expected).

The number of deaths from malignant neoplasms as a group was less than expected (SMR 87), and there were no significant increases in mortality from particular cancers, with or without taking a 15 year latency period into account. Deaths from lung cancer were not in excess (SMR 82), and none were reported from cancer of the liver or gall bladder, although only 0.5 had been expected. There were no deaths from cancer of the connective tissues and just one of the kidney vs. 0.7 expected. Non-malignant diseases of the blood and blood-forming organs caused no deaths, nor were deaths attributed to diseases of the liver besides cirrhosis, for which observed and expected deaths were equal (SMR 103). Mortality from respiratory diseases was also not increased (SMR 101).

Plant-specific mortality data are presented in Tables 3-6. Deaths due to accidents, poisonings, and violence were elevated only at Radford. All of these deaths occurred following termination of employment. Mortality from all causes (SMRs 125 and 133, 95% confidence limits 85-177 and 109-154 at Radford and Joliet, respectively), however, and mortality from circulatory system diseases (SMRs 126 and 143, 95% confidence limits 65-234 and 112-179, respectively) were in excess at both plants. The preponderance of excess circulatory system deaths resulted from ischemic heart disease and residual diseases of the circulatory system, which include causes of death that may

share an atherogenic etiology with ischemic heart disease, such as congestive failure (4 deaths), cardiac arrest (3 deaths), and arteriosclerosis (1 death). In contrast, cerebrovascular mortality was not increased; and no underlying cause of death was ascribed to hypertensive disease, diabetes mellitus, or cardiomyopathy. Of 64 deaths from ischemic heart disease, hypertensive disease and diabetes mellitus were noted as contributing to the cause of only 8 and 4, respectively; congestive heart failure, a clinical hallmark of cardiomyopathy, was mentioned in just 4 cases.

Persons living in areas surrounding the Joliet and Radford plants at most ages experience greater mortality from ischemic heart disease than the U.S. general population.[13] Age-specific mortality rates for white males of the counties in which the plants are located (Montgomery and Pulaski counties including the city of Radford, Virginia, and Will County, Illinois), therefore, were obtained for the years 1968-1978 inclusive (Table 7). These rates were applied to the person-years accumulated by the cohorts during the same period to determine the numbers of deaths expected from ischemic heart disease had the experience of the cohorts been identical with that of the local populations. When observed and expected deaths were tallied using local county experience as the standard, mortality from ischemic heart disease remained high at both plants (SMRs 133 and 138 at Joliet and Radford, 95% confidence limits 53-275 and 96-193, respectively). The combined SMR was statistically significant (SMR 137, $p=0.05$).

The death certificates of 56 of the 64 persons who had died from ischemic heart disease indicated that death was caused by myocardial infarction, coronary thrombosis or occlusion, or acute coronary or myocardial insufficiency. In 30 of 37 such death

certificates on which the interval between onset of the precipitating event and death was recorded death supervened within a day, 15 within minutes. The causes of non-violent deaths which occur soon after onset of the precipitating event are more likely to be misdiagnosed on death certificates. Twenty of the 30 deaths which occurred within a day, however, took place in hospitals or nursing homes or were certified by physicians who had attended the deceased for years. The medical circumstances of these deaths, therefore, were probably known to the physicians who completed the death certificates.

The median age at death from ischemic heart disease was 61. Only one person died from ischemic heart disease while employed at a job with potential for DNT exposure. Death usually occurred many years after the individual had ceased to work at the plant since duration of employment was generally short due to the fact that opportunity for work in peacetime was limited. The median duration of employment of cohort members was only 2.1 years at Joliet and 1.8 years at Radford; and the median length of employment in jobs with potential for DNT exposure was 0.4 and 1.2 years, respectively. Just one individual at Joliet and 9 at Radford had worked in DNT-related jobs for more than 5 years.

A histogram in Figure 1 depicts the combined SMRs for circulatory system diseases by years since entry into the cohorts. Each bar is based on a minimum of 5 expected deaths computed using U.S. rates. During the first ten years following entry into the cohorts mortality from circulatory system diseases was low (SMR 41). It then rose sharply, reaching a plateau (~ SMR 150) when 15-20 years had elapsed. The pattern of lower mortality in the first 15 years followed by higher mortality thereafter was observed at each plant (Table 8) for all circulatory system diseases

(observed/expected deaths: 0/3.1 vs. 14/8.0 and 7/7.1 vs. 66/44.1 at Joliet and Radford, respectively), for ischemic heart disease (0/2.2 vs. 11/6.2 and 4/4.3 vs. 49/32.8), and for residual diseases of the circulatory system (0/0.4 vs. 2/0.9 and 0/1.5 vs. 11/5.4).

When age and calendar year distributions of mortality experience differ, however, as with mortality during early and later years, comparison of SMRs may be misleading. Discrepancies might arise simply as a result of differences in the relative size of various age and calendar year strata, although stratum-specific mortality could be identical. Observed age-specific mortality rates for ischemic heart disease among the combined cohorts more than 15 years following entry into the study, therefore, were applied to the person-year distribution of the first 15 years. The resulting number of deaths was more than twice that observed during those 15 years (8.2 vs. 4 deaths), suggesting that dissimilarities of age distribution could not account for the increased SMR from ischemic heart disease noted later. Differences in calendar years of observation, likewise, would have had little effect on SMRs. The mean year of death from ischemic heart disease more than 15 years since entry into the study was 1972. If age-specific U.S. mortality rates for 1970-1974 had been applied to the person-year distribution of experience in the first 15 years of the study, 6.4 deaths would have been expected, as opposed to 6.5, using rates of the appropriate calendar years.

Evidence that cohort members had not been in poor health close to the time they began working at the plant was obtained from Selective Service System classification records located for 250 of the Radford cohort at the Washington National Record Center in Suitland, Maryland. Among persons undergoing first physical examinations to

determine eligibility for military service during the period November 1940 - December 1943. 32.9% (24/73) of cohort members were disqualified compared to 33.2% of Virginia white males.[14] Five percent (1/20) of examinations and reexaminations conducted among cohort members from August 1944 - August 1945 resulted in rejection. compared to a rejection rate of 6.0% in Virginia white males.[15]

The effect of duration of exposure on mortality from ischemic heart disease more than 15 years following cohort entry was evaluated by comparing persons with relatively brief exposure to the others. Duration of exposure to DNT at Joliet prior to the 1950s was estimated from information provided on employment applications. Only 4 persons indicated having worked previously at DNT manufacturing jobs. The shortest exposure period in months that would yield at least 5 expected deaths among the Radford cohort was 5 months. Within duration categories of more or less than 5 months of exposure the effect of exposure intensity was examined at Radford. (This was not possible to do at Joliet because workers there had been exposed to only high levels of DNT). Persons employed at DNT-related jobs with only high exposure were compared to those who had held a mixture of jobs with low, moderate, or high levels of DNT exposure and whose overall exposure intensity was less. Median exposure durations among groups with 5 months or less were 2.6 months at Joliet and 2.8 or 3.9 months at Radford for persons with only high or with mixed intensities of exposure. Among those whose exposure had exceeded 5 months, median durations were 0.8, 1.2, and 1.4 years, respectively.

Table 9 presents the data relating duration and intensity of exposure to mortality from ischemic heart disease more than 15 years following entry into the cohorts. In all strata of exposure intensity men who had worked at DNT-related jobs for 5 months or

less had lower SMRs than those employed for longer periods. Within both categories of exposure duration persons who had held a mixture of jobs affording low, moderate, or high levels of exposure despite greater median exposure durations had lower SMRs than individuals whose DNT-related work experience had included only jobs with high exposure. SMRs of men with high exposure were similar at both plants in each duration category. Overall the mortality of persons exposed 5 months or less did not differ from expected (SMR 103), whereas that of persons exposed at greater length was significantly elevated (SMR 168, $p \leq 0.001$). These results suggest the existence of a dose response relationship.

DISCUSSION

The mortality risk of workers, especially from heart disease, is commonly lower than that of the general population. This phenomenon, termed "the healthy worker effect", has been ascribed to selection pressures which reduce the likelihood that ill and disabled individuals will enter or stay in the workforce. Because only working persons are eligible for admission to an occupational cohort, the healthy worker effect is greatest at the time of cohort identification. Thereafter it diminishes in intensity, for cohort members need not continue working in order to be retained in a study. Whereas cancer is apt to remain silent throughout a long latent period, the clinical manifestations of underlying heart disease are more readily apparent. Heart disease, therefore, is much more likely than cancer to be selected against in the recruitment and retention of an active workforce.[16]

In this study, however, workers at two plants linked only by exposure to DNT experienced excessive mortality from heart disease. None of the Joliet cohort and few from Radford had held jobs where there might have been opportunity for exposure to

nitroglycerin or ethylene glycol dinitrate, munitions compounds previously associated with heart disease.[17] Since the pathogenesis of the disease reported here is undoubtedly related to coronary atherosclerosis, the frequency and severity of illness should be affected by the distribution of the known risk factors for coronary atherosclerosis, such as blood pressure, blood lipids, diabetes mellitus, smoking, alcohol consumption, psychosocial influences, and physical activity.[18] It is unlikely, however, that an aggregation of known risk factors independent of exposure could explain the observed results.

The importance of several risk factors is doubtful. Hypertension and diabetes may have played only minor roles since they were infrequently mentioned on death certificates; furthermore, cerebrovascular mortality, for which hypertension is the principal determinant,[19] was not elevated. Mortality from lung cancer, a marker for cigarette smoking, was less than expected; and deaths due to respiratory diseases were not increased. Ammunition workers, moreover, are forbidden to smoke on the job. For these reasons the proportion of heavy smokers among the cohorts is probably not great. The extent and effect of consumption of alcoholic beverages by the study population is unclear. Cirrhosis of the liver, prominent among causes of death in alcoholics, was not in excess; yet mortality from accidents, poisonings, and violence, also associated with alcoholism, was significantly increased in the Radford cohort. While light to moderate drinking may protect against coronary heart disease, heavy drinking is detrimental.[20] It is not known which effect, if either, might predominate here.

The health of members of the Radford cohort near the time of cohort entry, as judged by performance on military physical examinations, appeared to be no different from that of others from the state of Virginia. Had the cohorts under study, nevertheless, possessed an abundance of atherogenic traits or living habits, the incidence among them of acute myocardial infarction should always have been elevated.[21] Instead at both plants mortality from ischemic heart disease during the first 15 years following cohort entry was less than expected, and it increased only in later years. Although the deficit in mortality during the initial period of observation may be attributed to the healthy worker effect - namely, that on admission to the study these individuals had less risk for heart disease than the general population - loss of the healthy worker effect in itself cannot explain the subsequent mortality excess. The excess remained even when comparison was made to the number of deaths expected using local county mortality as the standard. Increased mortality following a latent period is characteristic of a chronic occupational disease, and there is suggestive evidence of a relationship with duration and intensity of exposure. Men who had worked 5 months or less at jobs with potential for DNT exposure had a more favorable mortality experience than those employed for longer periods. Within categories of exposure duration individuals whose DNT-related work experience had included only jobs with high exposure had larger SMRs than persons who had held a mixture of jobs affording low, moderate, or high levels of exposure and whose overall exposure intensity was less.

It would be difficult to account for the heart disease observations on the basis of chance alone or an increase in cardiovascular risk factors. Due to "the healthy worker effect", occupational cohorts almost never exhibit increased mortality from heart disease. Yet here two cohorts at plants in different states selected as the result of exposure to

DNT demonstrated substantial excesses. While chance or an increase in risk factors would be unlikely to explain the existence of a latency period and an apparent dose response relationship, the latter are commonly observed with chronic occupational diseases. Several of the known risk factors appear not to have been in excess. Had there been increased risk for heart disease, health near the time of cohort entry might have been impaired and reflected in the results of military physical examinations and in mortality during the initial period of observation, not just after 15 years. Although death generally occurred many years following the last exposure and the period of exposure was brief, these facts are consistent with a biological explanation involving atherosclerotic plaque formation initiated by direct chemical damage to the coronary arteries. Such an hypothesis has been proposed by Benditt.[22] It is possible, but not probable, that occupational exposure(s) besides DNT might have been the etiological agent(s). DNT was the only exposure common to both plant cohorts, and duration and intensity of DNT exposure correlated with extent of mortality from ischemic heart disease.

All deaths from accidents, poisonings, and violence occurred after termination of plant employment, not during employment as might be expected if they had resulted from chemical narcosis. Increased risk was found only among the Radford cohort. A study of a different cohort at the Radford plant, with little opportunity for DNT exposure, also revealed elevated mortality from external causes.[23] This excess mortality, therefore, is apt to be the consequence of the lifestyle of Radford workers and not occupational exposures.

Were DNT, in fact, a human carcinogen, it was unlikely that significant increases in such rare tumors as cancers of the liver, gallbladder, kidney, or connective tissues would be observed in this study. For cancers of the liver and gallbladder, for example, only an eightfold or greater increase in risk (one-tailed $p \leq 0.05$) should have been detected (80% power). It must be recognized that this estimate does not consider whether the workers had experienced adequate exposures or latency periods for developing these malignancies; furthermore, the power of the study would be reduced considerably if only the 2,6-isomer were carcinogenic since very little was present in the DNT used at Radford. While the results do not exclude the possibility that DNT may yet cause human cancer, exposed workers should be reassured that a great increase in risk is unlikely and the risk itself is small.

This investigation was undertaken to determine whether the carcinogenicity of DNT in rodent bioassays had relevance for man. No evidence of a carcinogenic effect was found. An unexpected excess was noted of mortality from ischemic heart disease. Treatment-related cardiovascular lesions had not been reported in rat or mouse bioassays, but these species are resistant to naturally occurring or experimentally induced atherosclerosis.[24] Epidemiological investigations of other heavily exposed human populations are needed to confirm the etiological significance of the association described here. Laboratory documentation of an effect on the coronary arteries should also be pursued using suitable nonhuman primate experimental models.

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Figure Legends

FIGURE 1. Standardized mortality ratios for circulatory system diseases by years since entry into the combined cohorts.

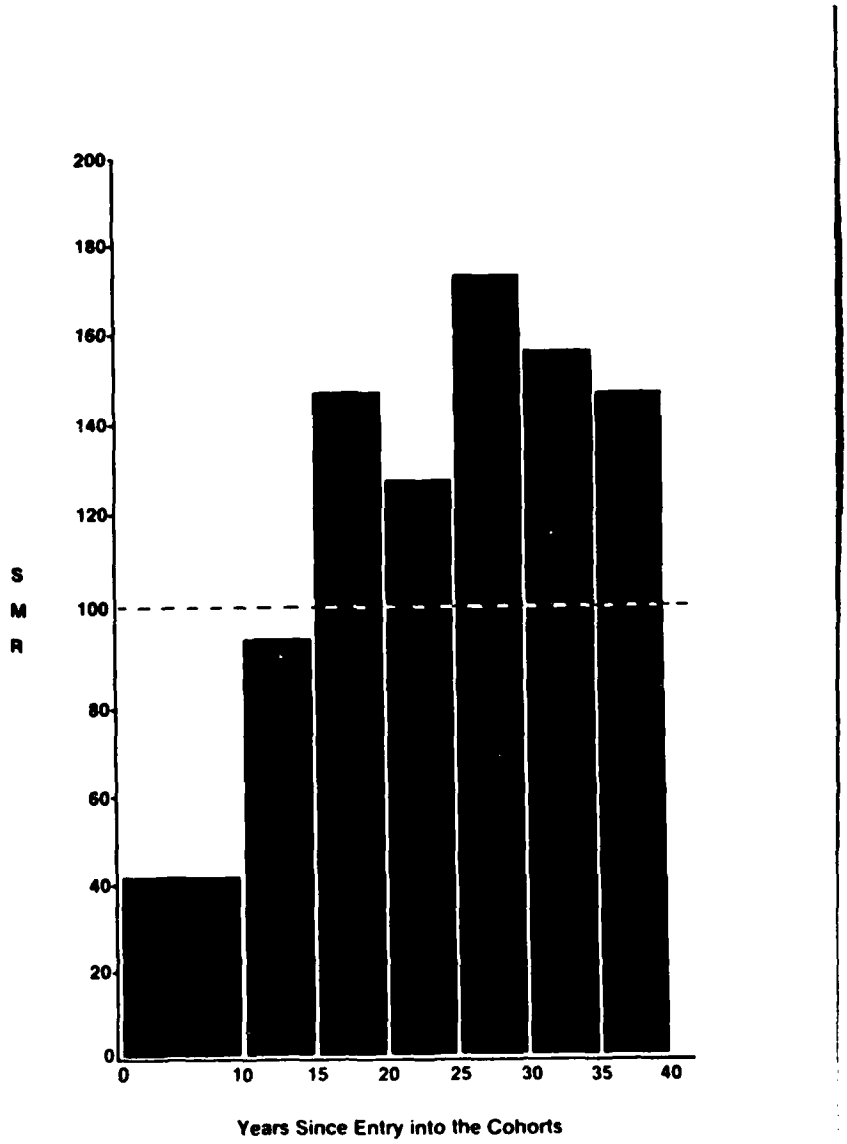

Table 1

MORTALITY OF THE COMBINED COHORTS

Cause of death (8th Revision, ICDA)	O	E	SMR	95% Confidence Limits on the SMR	
				Lower Limit	Upper Limit
All causes	164	127.3	129***	110	150
All malignant neoplasms (140-209)	22	25.4	87	54	131
Buccal cavity & pharynx (140-149)	0	0.9	---§	---§	---§
Digestive system (150-159)	9	6.9	131	60	249
Esophagus (150)	1	0.6	---	---	---
Stomach (151)	1	1.3	---	---	---
Colon (153)	4	2.2	186	50	475
Rectum (154)	0	0.8	---	---	---
Liver & gall bladder (155-156)	0	0.5	---	---	---
Pancreas (157)	2	1.4	---	---	---
Respiratory system (160-163)	7	9.0	78	31	161
Lung (162)	7	8.5	82	33	170
Bone (170)	0	0.1	---	---	---
Skin (172-173)	1	0.5	---	---	---
Prostate (185)	1	1.2	---	---	---
Urinary organs (188-189)	2	1.3	---	---	---
Kidney (189)	1	0.7	---	---	---
Brain & central nervous sys. (191-192)	1	0.9	---	---	---
Lymphatic & hematopoietic sys. (200-209)	1	2.6	---	---	---
Leukemia (204-207)	0	1.0	---	---	---
Other cancers	0	2.0	---	---	---
All non-malignant diseases (000-136,210-796)	114	86.9	131**	108	158
Infectious & parasitic (000-136)	2	2.4	---§	---§	---§
Endocrine, nutrit. & metabolic (240-279)	0	2.0	---	---	---
Circulatory system (390-458)	87	62.3	140**	112	172
Chronic rheumatic heart dis. (393-398)	3	1.6	183	37	534
Ischemic heart disease (410-414)	64	45.5	141**	108	180
Cerebrovascular disease (430-438)	7	7.0	100	40	206
Residual circulatory system	13	8.2	159	84	271
Respiratory system (460-519)	7	7.0	101	40	207
Pneumonia (480-486)	2	2.5	---	---	---
Emphysema (492)	2	1.8	---	---	---
Digestive system (520-577)	10	7.0	142	68	261
Cirrhosis of the liver (571)	4	3.9	103	28	264
Genitourinary system (580-629)	4	1.7	233	63	596
Chronic nephritis (582)	1	0.7	---	---	---
Other non-malignant disease	4	4.4	91	24	233
Accidents, poisonings, violence (E800-E999)	28	14.6	191***	127	276
Residual	0	0.4	---	---	---

O - observed deaths E - expected deaths SMR - standardized mortality ratio

**p ≤ 0.01 ***p ≤ 0.001

§SMRs given only when observed or expected deaths ≥ 3

Table 2

MORTALITY OF THE COMBINED COHORTS MORE THAN 15 YEARS FOLLOWING COHORT ENTRY

Cause of death (8th Revision, ICDA)	O	E	SMR	95% Confidence Limits on the SMR	
				Lower Limit	Upper Limit
All causes	140	99.9	140****	118	165
All malignant neoplasms (140-209)	20	21.5	93	57	144
Buccal cavity & pharynx (140-149)	0	0.8	---§	---§	---§
Digestive system (150-159)	7	5.7	122	49	252
Esophagus (150)	1	0.5	---	---	---
Stomach (151)	1	1.0	---	---	---
Colon (153)	4	1.9	217	58	554
Rectum (154)	0	0.6	---	---	---
Liver & gall bladder (155-156)	0	0.4	---	---	---
Pancreas (157)	1	1.2	---	---	---
Respiratory system (160-163)	7	8.1	87	35	179
Lung (162)	7	7.6	92	37	189
Bone (170)	0	0.1	---	---	---
Skin (172-173)	1	0.4	---	---	---
Prostate (185)	1	1.1	---	---	---
Urinary organs (188-189)	2	1.2	---	---	---
Kidney (189)	1	0.6	---	---	---
Brain & central nervous sys. (191-192)	1	0.7	---	---	---
Lymphatic & hematopoietic sys. (200-209)	1	2.0	---	---	---
Leukemia (204-207)	0	0.8	---	---	---
Other cancers	0	1.6	---	---	---
All non-malignant diseases (000-136,210-796)	102	70.3	145***	118	176
Infectious & parasitic (000-136)	1	0.9	---§	---§	---§
Endocrine, nutrit. & metabolic (240-279)	0	1.7	---	---	---
Circulatory system (390-458)	80	52.1	153****	122	191
Chronic rheumatic heart dis. (393-398)	2	1.0	---	---	---
Ischemic heart disease (410-414)	60	39.0	154***	117	198
Cerebrovascular disease (430-438)	5	5.9	85	27	199
Residual circulatory system	13	6.2	208**	112	359
Respiratory system (460-519)	7	5.9	120	48	247
Pneumonia (480-486)	2	1.9	---	---	---
Emphysema (492)	2	1.7	---	---	---
Digestive system (520-577)	9	5.4	167	76	318
Cirrhosis of the liver (571)	4	3.1	128	34	327
Genitourinary system (580-629)	2	1.1	---	---	---
Chronic nephritis (582)	0	0.4	---	---	---
Other non-malignant disease	3	3.3	91	18	266
Accidents, poisonings, violence (E800-E999)	18	7.9	228***	135	361
Residual	0	0.2	---	---	---

O - observed deaths E - expected deaths SMR - standardized mortality ratio

**p ≤ 0.01 ***p ≤ 0.001 ****p ≤ 0.0001

§SMRs given only when observed or expected deaths ≥ 3

Table 3

MORTALITY OF THE JOLIET COHORT

Cause of death (8th Revision, ICDA)	O	E	SMR	95% Confidence Limits on the SMR	
				Lower Limit	Upper Limit
All causes	31	24.9	125	85	177
All malignant neoplasms (140-209)	7	4.9	142	57	293
Buccal cavity & pharynx (140-149)	0	0.2	---§	---§	---§
Digestive system (150-159)	3	1.2	248	50	725
Esophagus (150)	1	0.1	---	---	---
Stomach (151)	1	0.2	---	---	---
Colon (153)	0	0.4	---	---	---
Rectum (154)	0	0.1	---	---	---
Liver & gall bladder (155-156)	0	0.1	---	---	---
Pancreas (157)	1	0.3	---	---	---
Respiratory system (160-163)	1	1.0	---	---	---
Lung (162)	1	1.7	---	---	---
Bone (170)	0	0.0	---	---	---
Skin (172-173)	1	0.1	---	---	---
Prostate (185)	1	0.1	---	---	---
Urinary organs (188-189)	1	0.2	---	---	---
Kidney (189)	0	0.1	---	---	---
Brain & central nervous sys. (191-192)	0	0.2	---	---	---
Lymphatic & hematopoietic sys. (200-209)	0	0.6	---	---	---
Leukemia (204-207)	0	0.2	---	---	---
Other cancers	0	0.4	---	---	---
All non-malignant diseases (000-136,210-796)	21	15.0	133	82	203
Infectious & parasitic (000-136)	0	0.3	---§	---§	---§
Endocrine, nutrit. & metabolic (240-279)	0	0.4	---	---	---
Circulatory system (390-458)	14	11.1	126	69	211
Chronic rheumatic heart dis. (393-398)	0	0.3	---	---	---
Ischemic heart disease (410-414)	11	8.4	131	65	234
Cerebrovascular disease (430-438)	1	1.1	---	---	---
Residual circulatory system	2	1.3	---	---	---
Respiratory system (460-519)	2	1.1	---	---	---
Pneumonia (480-486)	1	0.4	---	---	---
Emphysema (492)	1	0.3	---	---	---
Digestive system (520-577)	2	1.6	---	---	---
Cirrhosis of the liver (571)	1	1.0	---	---	---
Genitourinary system (580-629)	0	0.3	---	---	---
Chronic nephritis (582)	0	0.1	---	---	---
Other non-malignant disease	3	1.0	300	60	877
Accidents, poisonings, violence (E800-E999)	3	4.1	74	15	215
Residual	0	0.1	---	---	---

O - observed deaths E - expected deaths SMR - standardized mortality ratio

§SMRs given only when observed or expected deaths ≥ 3

Table 4

MORTALITY OF THE JOLIET COHORT MORE THAN 15 YEARS FOLLOWING COHORT ENTRY

Cause of death (8th Revision, ICDA)	O	E	SMR	95% Confidence Limits on the SMR	
				Lower Limit	Upper Limit
All causes	28	16.6	169**	112	244
All malignant neoplasms (140-209)	6	3.6	165	60	360
Buccal cavity & pharynx (140-149)	0	0.1	---§	---§	---§
Digestive system (150-159)	2	0.9	---	---	---
Esophagus (150)	1	0.1	---	---	---
Stomach (151)	1	0.1	---	---	---
Colon (153)	0	0.3	---	---	---
Rectum (154)	0	0.1	---	---	---
Liver & gall bladder (155-156)	0	0.1	---	---	---
Pancreas (157)	1	0.2	---	---	---
Respiratory system (160-163)	1	1.4	---	---	---
Lung (162)	1	1.4	---	---	---
Bone (170)	0	0.0	---	---	---
Skin (172-173)	1	0.1	---	---	---
Prostate (185)	1	0.1	---	---	---
Urinary organs (188-189)	1	0.2	---	---	---
Kidney (189)	0	0.1	---	---	---
Brain & central nervous sys. (191-192)	0	0.1	---	---	---
Lymphatic & hematopoietic sys. (200-209)	0	0.4	---	---	---
Leukemia (204-207)	0	0.1	---	---	---
Other cancers	0	0.3	---	---	---
All non-malignant diseases (000-136,210-796)	20	11.1	181**	110	278
Infectious & parasitic (000-136)	0	0.1	---§	---§	---§
Endocrine, nutrit. & metabolic (240-279)	0	0.3	---	---	---
Circulatory system (390-458)	14	8.0	175*	96	244
Chronic rheumatic heart dis. (393-398)	0	0.2	---	---	---
Ischemic heart disease (410-414)	11	6.2	178	89	318
Cerebrovascular disease (430-438)	1	0.8	---	---	---
Residual circulatory system	2	0.9	---	---	---
Respiratory system (460-519)	2	0.8	---	---	---
Pneumonia (480-486)	1	0.3	---	---	---
Emphysema (492)	1	0.2	---	---	---
Digestive system (520-577)	2	1.1	---	---	---
Cirrhosis of the liver (571)	1	0.7	---	---	---
Genitourinary system (580-629)	0	0.1	---	---	---
Chronic nephritis (582)	0	0.1	---	---	---
Other non-malignant disease	2	0.7	---	---	---
Accidents, poisonings, violence (E800-E999)	2	1.9	---	---	---
Residual	0	0.0	---	---	---

O - observed deaths E - expected deaths SMR - standardized mortality ratio

*$p \leq 0.05$ **$p \leq 0.01$

§SMRs given only when observed or expected deaths ≥ 3

Table 5

MORTALITY OF THE RADFORD COHORT

Cause of death (8th Revision, ICDA)	O	E	SMR	95% Confidence Limits on the SMR	
				Lower Limit	Upper Limit
All causes	133	102.4	130**	109	154
All malignant neoplasms (140-209)	15	20.5	73	41	121
Buccal cavity & pharynx (140-149)	0	0.7	---§	---§	---§
Digestive system (150-159)	6	5.7	106	39	231
Esophagus (150)	0	0.5	---	---	---
Stomach (151)	0	1.1	---	---	---
Colon (153)	4	1.8	226	61	578
Rectum (154)	0	0.7	---	---	---
Liver & gall bladder (155-156)	0	0.4	---	---	---
Pancreas (157)	1	1.1	---	---	---
Respiratory system (160-163)	6	7.2	83	30	182
Lung (162)	6	6.8	88	32	192
Bone (170)	0	0.1	---	---	---
Skin (172-173)	0	0.4	---	---	---
Prostate (185)	0	1.0	---	---	---
Urinary organs (188-189)	1	1.1	---	---	---
Kidney (189)	1	0.5	---	---	---
Brain & central nervous sys. (191-192)	1	0.7	---	---	---
Lymphatic & hematopoietic sys. (200-209)	1	2.0	---	---	---
Leukemia (204-207)	0	0.8	---	---	---
Other cancers	0	1.0	---	---	---
All non-malignant diseases (000-136,210-796)	93	71.0	131**	106	160
Infectious & parasitic (000-136)	2	2.1	---§	---§	---§
Endocrine, nutrit. & metabolic (240-279)	0	1.0	---	---	---
Circulatory system (390-458)	73	51.2	143**	112	179
Chronic rheumatic heart dis. (393-398)	3	1.3	229	46	668
Ischemic heart disease (410-414)	53	37.1	143**	107	187
Cerebrovascular disease (430-438)	6	5.9	101	37	220
Residual circulatory system	11	6.9	160	79	285
Respiratory system (460-519)	5	5.8	86	28	201
Pneumonia (480-486)	1	2.0	---	---	---
Emphysema (492)	1	1.5	---	---	---
Digestive system (520-577)	8	5.5	146	63	288
Cirrhosis of the liver (571)	3	2.9	104	21	304
Genitourinary system (580-629)	4	1.4	278	75	710
Chronic nephritis (582)	1	0.6	---	---	---
Other non-malignant disease	1	3.4	29	38	164
Accidents, poisonings, violence (E800-E999)	25	10.6	237****	153	349
Residual	0	0.3	---	---	---

O - observed deaths E - expected deaths SMR - standardized mortality ratio

**p ≤ 0.01 ****p ≤ 0.0001

§SMRs given only when observed or expected deaths ≥ 3

Table 6

MORTALITY OF THE RADFORD COHORT MORE THAN 15 YEARS FOLLOWING COHORT ENTRY

Cause of death (8th Revision, ICDA)	O	E	SMR	95% Confidence Limits on the SMR	
				Lower Limit	Upper Limit
All causes	112	83.3	134**	111	162
All malignant neoplasms (140-209)	14	17.9	78	43	131
Buccal cavity & pharynx (140-149)	0	0.6	---§	---§	---§
Digestive system (150-159)	5	4.8	103	33	241
Esophagus (150)	0	0.5	---	---	---
Stomach (151)	0	0.8	---	---	---
Colon (153)	4	1.6	257	69	658
Rectum (154)	0	0.5	---	---	---
Liver & gall bladder (155-156)	0	0.3	---	---	---
Pancreas (157)	1	1.0	---	---	---
Respiratory system (160-163)	6	6.6	91	33	197
Lung (162)	6	6.3	96	35	208
Bone (170)	0	0.1	---	---	---
Skin (172-173)	0	0.3	---	---	---
Prostate (185)	0	1.0	---	---	---
Urinary organs (188-189)	1	1.0	---	---	---
Kidney (189)	1	0.5	---	---	---
Brain & central nervous sys. (191-192)	1	0.5	---	---	---
Lymphatic & hematopoietic sys. (200-209)	1	1.7	---	---	---
Leukemia (204-207)	0	0.6	---	---	---
Other cancers	0	1.3	---	---	---
All non-malignant diseases (000-136,210-796)	82	59.2	139**	110	172
Infectious & parasitic (000-136)	1	0.8	---§	---§	---§
Endocrine, nutrit. & metabolic (240-279)	0	1.4	---	---	---
Circulatory system (390-458)	66	44.1	150***	116	190
Chronic rheumatic heart dis. (393-398)	2	0.9	---	---	---
Ischemic heart disease (410-414)	49	32.8	149**	110	197
Cerebrovascular disease (430-438)	4	5.1	78	21	200
Residual circulatory system	11	5.4	206*	102	365
Respiratory system (460-519)	5	5.0	100	32	232
Pneumonia (480-486)	1	1.6	---	---	---
Emphysema (492)	1	1.5	---	---	---
Digestive system (520-577)	7	4.3	163	65	335
Cirrhosis of the liver (571)	3	2.4	124	25	363
Genitourinary system (580-629)	2	0.9	---	---	---
Chronic nephritis (582)	0	0.3	---	---	---
Other non-malignant disease	1	2.7	---	---	---
Accidents, poisonings, violence (E800-E999)	16	6.0	265****	152	431
Residual	0	0.1	---	---	---

O - observed deaths E - expected deaths SMR - standardized mortality ratio

* $p \leq 0.05$ ** $p \leq 0.01$ *** $p \leq 0.001$ **** $p \leq 0.0001$

§SMRs given only when observed or expected deaths ≥ 3

Table 7

DEATH RATES FROM ISCHEMIC HEART DISEASE PER 100,000 WHITE MALES BY AGE

1968 - 1978

Age	Montgomery & Pulaski Counties, Virginia	Will County, Illinois	U.S.A.
15-	0.0	0.0	0.3
20-	2.1	0.0	0.8
25-	4.5	1.8	2.9
30-	13.0	12.1	11.4
35-	27.4	31.5	40.1
40-	149.9	121.9	106.8
45-	354.3	245.7	223.0
50-	494.3	403.9	393.3
55-	882.1	645.5	653.4
60-	1309.8	1112.2	1031.0
65-	1981.5	1701.2	1540.5
70-	2466.4	2599.0	2285.7
75-84	4339.8	4959.9	4048.2

Table 8

ALL CAUSE AND CIRCULATORY SYSTEM MORTALITY BY YEARS SINCE ENTRY INTO THE COHORTS

Cause of Death (8th Revision, ICDA)	Observed (O) and Expected (E) Deaths and SMRs					
	0-15 Yr Since Entry			> 15 Yr Since Entry		
	O	E	SMR	O	E	SMR
JOLIET						
All causes	3	8.3	36	28	16.6	169**
Circulatory system (390-458)	0	3.1	0	14	8.0	175*
Chronic rheumatic heart dis. (393-398)	0	0.1	---§	0	0.2	---
Ischemic heart disease (410-414)	0	2.2	---	11	6.2	178
Cerebrovascular disease (430-438)	0	0.3	---	1	0.8	---
Residual circulatory system	0	0.4	---	2	0.9	---
RADFORD						
All causes	21	19.1	110	112	83.3	134**
Circulatory system (390-458)	7	7.1	99	66	44.1	150***
Chronic rheumatic heart dis. (393-398)	1	0.5	---	2	0.9	---
Ischemic heart disease (410-414)	4	4.3	93	49	32.8	149**
Cerebrovascular disease (430-438)	2	0.8	---	4	5.1	78
Residual circulatory system	0	1.5	---	11	5.4	206*

*$p \leq 0.05$ **$p \leq 0.01$ ***$p \leq 0.001$

§SMRs given only when observed or expected deaths ≥ 3

Table 9

MORTALITY FROM ISCHEMIC HEART DISEASE MORE THAN 15 YEARS FOLLOWING COHORT ENTRY BY EXPOSURE DURATION AND INTENSITY

		Exposure Duration					
		≤ 5 Months		> 5 Months		Total	
Plant	Exposure Intensity	O/E	SMR	O/E	SMR	O/E	SMR
Joliet	High	4/3.1	131	7/3.1	224*	11/6.2	178
Radford	Only High	5/3.7	135	10/4.9	205*	15/8.6	175*
	Mixed	0/1.9	---§	34/22.3	153*	34/24.2	140
	Total	9/8.7	103	51/30.3	168***	60/39.0	154***

*p≤0.05 ***p≤0.001

§SMRs given only when observed or expected deaths ≥ 3

APPENDIX

RADFORD JOBS WITH OPPORTUNITY FOR DNT EXPOSURE CATEGORIZED BY EXPOSURE INTENSITY

Code		
CIIT	Radford	Job Title
High Exposure:		
015	ADRH	air dry helper
016	ADRO	air dry operator
043	AUXO	auxiliary operator
044		chief auxiliary operator
045		bag cleaning house operator
134	CBCO	chemical preparation chief operator
135	CHPO	chemical preparation operator
142	COHH	coating house helper
143	COTO	coating house operator
183	DNTO	DNT screen house
212	FMHH	final mix helper
214	FIMO	final mix operator
224	FSCO	finishing area operator (coating house)
499	SCBO	screen burner operator
500		screen cleaner operator
501	SCHH	screen house helper
502	SCRO	screen house operator
Moderate Exposure:		
074	BLHH	blending house helper
075	BLHO	blending house operator
136	CLNH	cleanup helper
213	FMHF	final mix house foreman
222	FARO	finishing area operator
223	FABO	finishing area operator (blender)
225	FSGO	finishing area operator (glaze house)
226	FSCO (FSSO)	finishing area operator (screen house)
251	GLZH	glaze house helper
252	GLZO	glaze house operator
441	PRBO	preblender operator

RADFORD JOBS WITH OPPORTUNITY FOR DNT EXPOSURE CATEGORIZED
BY EXPOSURE INTENSITY (cont'd)

Code		
CIIT	Radford	Job Title
Low Exposure:		
014	ADAF	air dry area foreman
026	AMCA	area mechanic A
027	AMCB	area mechanic B
028	AMCC	area mechanic C
090	BPHO	box pack house operator
107	CPHH	can pack house helper
108	CPHO	can pack house operator
109		can pack operator
133	CSBF	chemical preparation & screen burning house foreman
167	CUTO	cutting house operator
211	FMAF	final mix area foreman
227	FPHF	finishing press house foreman
314	MCRH	macaroni helper
315	MACO	macaroni operator
316		macaroni press operator
442	PBLO	preblocker operator
443		preblocker press operator
450	FPOP	press house operator
451	PRSO	press man operator
476		rest house operator
511	SMKH	smokeless helper
530	SOPO	solvent powder operator
535	SRHF	sorting house foreman
536	SRHH	sorting house helper
537		sorting house operator
604	WDAH	water dry helper
605	WDRO	water dry operator
621	PRSO	final press operator

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1	National Institute for Occupational Safety and Health Division of Surveillance Hazard Evaluations and Field Studies Mail Stop 16 4676 Columbia Parkway Cincinnati, OH 45226
1	Office of the Surgeon General ATTN: DASG-PSPE Skyline Place No. 5 5111 Leesburg Pike Falls Church, VA 22041-3258
1	Commander US Army Material Command ATTN: AMCSG 5001 Eisenhower Ave. Alexandria, VA 22333
1	Commander US Army Armaments, Munitions and Chemical Command ATTN: AMSMC-SG Rock Island, IL 61299-5000

1 Director
Walter Reed Army Institute of Research
ATTN: SGRD-UWK
Division of Preventive Medicine
Washington, DC 20307-5200

1 Commander
US Army Radford Army Ammunition Plant
ATTN: SMCRA-EN
Radford, VA 24141-0298

1 Commander
US Army Environmental Hygiene Agency
HSHD-AD-L
Aberdeen Proving Ground, MD 21010-5422